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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,774	03/13/2003	Tracey Brown	DACO:002US	2305
21874	7590	11/01/2005	EXAMINER	
EDWARDS & ANGELL, LLP P.O. BOX 55874 BOSTON, MA 02205			BERKO, RETFORD O	
			ART UNIT	PAPER NUMBER
			1618	

DATE MAILED: 11/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/088,774	BROWN ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Retford Berko	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 27 July 2005.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 25-33,35-37 and 39-47 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 25-33,35-37 and 39-47 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |                                                                                                                        |                                                                                         |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                            | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____                                                |

### **DETAILED ACTION**

**Acknowledgement:** Applicant's Amendment filed 7/27/05 is acknowledged.

### **Status of Claims**

The status of the claims is as follows:

- (a) Claims 1-13 are cancelled in view of applicant's preliminary amendment filed March 13, 2004.
- (b) Claims 13-24 are cancelled by applicant.
- (c ) Claims 34 and 38 are cancelled by applicant.
- (d) Claims 25-33 and 35-37 and 39-47 remain pending for review.

### **Claim Rejections- 35 USC 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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Claims 25-33 and 35-37 and 39-47 remain rejected under 35 USC 103(a) as being unpatentable over Harper et al (US 5, 977, 088) in view of Faulk et al (US 5, 827, 834).

Harper (Patent '088) disclosed effective amounts of hyaluronic acid and/or salts or homologs applied to the skin to facilitate transport of medicines and therapeutic agents into skin sites of a pathology and/or trauma e.g. carcinoma (col 8, lin 60, col 9, lin 40-44, lin 60-65) for treatment of the condition in the skin (col 14, lin 32-45).

Harper does not teach pharmaceutical composition comprising hyaluronic acid for elimination of onset of metastases for oral administration.

Faulk (patent '834) disclosed administration of a therapeutic composition comprising hyaluronic acid and other drugs for treatment of patients (Examples at cols 20-22), col 13, lin 60; col 14, lin 20-30, col 15, lin 50-65, col 22, lin 25-45, col 29, lin 25; col 30, lin 30-40 and col 35, lin 1030). Faulk further disclosed the use of hyaluronic acid either before or after administration of antineoplastic agent (col 15, lin 50-65), suggesting that hyaluronic acid may improve the penetration or transport of drug (col 6, lin 60-65).

One of ordinary skill in the art would have been motivated to use a method of administering antineoplastic agent composition comprising hyaluronic acid and effective antineoplastic agents, e.g. 5-FU in order to obtain inhibition of cell proliferation because this was suggested by Harper (col 23, lin 45-67). One of ordinary skill would expect to obtain effective transport of the drugs to sites in order to obtain the antiproliferative effects of the agents used in combination with hyaluronic acid because hyaluronic acid is shown to improve penetration of drugs into cells or tissues (Faulk, Patent '834, col 13, lin 59-65 and col 14, lin 13-30). Therefore

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the invention as a whole would have been prima facie obvious to one of ordinary skill at the time that it was made.

### **Response To Arguments**

(1). Applicant did not present any argument in this amendment but requested that the changes in the claims should be entered. Examiner has complied.

Examiner reiterates the response to applicant's previous argument for the record only.

Applicant argues that specification does indeed support the use of hyaluronan to prevent metastasis (Example 4 and Fig. 6), that mice treated with hyaluronan showed a significant reduction in lymphoid metastasis, as compared to controls.

In response to this argument, Example 4 (Spec at page 38) shows the effect of hyaluronan on the in vitro efficacy of 5-FU to inhibit proliferation of cancer cells. Figure 6 shows the effect of hyaluronan and 5-FU in combination to inhibit metastasis in lymphoid tissue. The evidence is only a single example of the effectiveness of hyaluronan in enhancing the antineoplastic effect and reduction of metastasis and the usefulness for treatment of cancer in lymphoid tissue. However, the evidence is insufficient to support the generic claim—ie the effectiveness of hyaluronan in preventing cancer metastasis. Moreover, the prior art (Sakura et al ([Sho 61 (6191986)-17) discloses the cancer metastasis inhibitory effects of hyaluronan and cross-linked hyaluronan in mice.

Applicant argues that Sakura et al does not disclose a method in which metastasis is prevented, that the disclosure at most suggests a method and that the working examples of the reference do not support the methodology. Applicant contends that Sakura et al indicates

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hyalurotan inhibits binding of cells to tissue, renders the cells anchorage independent and thereby promotes metastasis.

In response, Sakura et al discloses that hyaluronic acid reduces bonding ability of tumor cells (page 16) and reduces the number of metastatic foci in lung in murine model (page 19).

Applicant's contention of the likelihood that hyalurotan inhibits binding of tumor cells to tissue, rendering the cells anchorage independent and thus likely promoting metastasis is not disclosed in the prior art reference.

Applicant argues that by amending claims 13 and 25 to recite a hyaluronan of molecular weight 750,000 daltons which is not taught in the prior art cited, the rejection of the claims under 35 USC 103 over Harper et al (US 5,977,088) in view of Faulk et al (US 5,827,834) should be withdrawn, that there is no basis for combining the two references as they use hyaluronic acid for different purposes and that the use of hyaluronic acid having molecular weight of less than 750,000 daltons is inconsistent with the claims that are drawn toward the use of hyaluronic acid of greater molecular weight.

In response to this argument, Patent '088 discloses that hyaluronic acid facilitates or causes the transport of medicine and/or therapeutic agent into the skin to the site of pathology and/or trauma (col 9, lin 60-65), providing the motivation to combine hyalurotan with other therapeutic agents in order to effect treatment due to increased bioavailability of drug to sites. Also, because the prior art discloses the use of hyaluronic acid in the composition, the burden shifts on applicant to show that molecular weight of the compound as claimed is critical.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

### Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Retford Berko** whose telephone number is 571-272-0590. The examiner can normally be reached on M-F from 8.00 am to 5.30 pm

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Thurman K Page**, can be reached on 571-272-0602.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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